Organic LETTERS

Letter

pubs.acs.org/OrgLett

Calcium-Catalyzed, Dehydrative, Ring-Opening Cyclizations of Cyclopropyl Carbinols Derived from Donor−Acceptor Cyclopropanes

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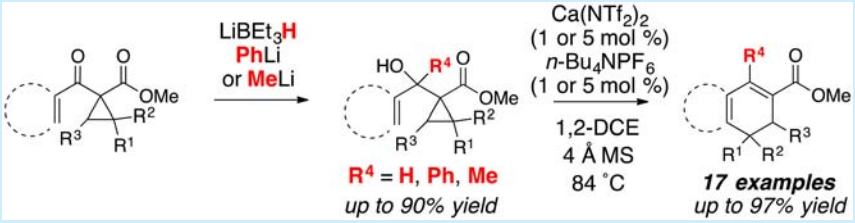
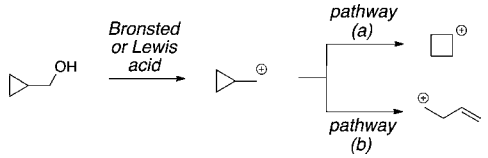
Supporting Information



ABSTRACT: A calcium-catalyzed, dehydrative, ring-opening cyclization of (hetero)aryl cyclopropyl carbinols is reported. The cyclopropyl carbinols are prepared directly from the corresponding donor−acceptor (D−A) cyclopropanes. The calcium catalyst catalyzes the formation of putative (hetero)aryl cyclopropyl carbinyl cations that undergo ring-opening to allylcarbinyl cations. Subsequent intramolecular Friedel−Crafts reaction affords (hetero)aryl-fused cyclohexa-1,3-dienes in up to 97% yield. This approach represents the first example of catalysis for this intramolecular, dehydrative ring-opening cyclization and outperforms the previous reports using stoichiometric Lewis acids.

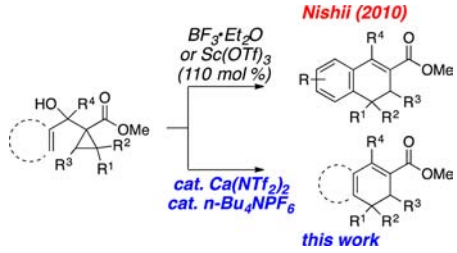
The cyclopropyl carbinol rearrangement provides a powerful example of the exploitation of inherent ring strain to effect ring expansion and opening (Scheme 1).[1] It proceeds through the formation of a putative cyclopropyl methylium followed by either ring expansion (via bond migration) to the cyclobutyl cation (pathway a) or ring opening to form a homoallyl cation (pathway b). These intermediates can readily be trapped by various nucleophiles or undergo eliminations to furnish more functionalized products.[2] The substituents around the cyclopropyl carbinol play a critical role in determining which pathway will be preferred, given their direct effect on the stabilization/destabilization of the resulting carbocation.[3] Despite their potential versatility as proelectrophiles, cyclopropyl carbinols have been somewhat understudied.

Scheme 1. General Acid-Mediated Reactivity of Cyclopropyl Carbinols



In a seminal report, in 2010, Nishii showed that aryl cyclopropyl carbinols undergo dehydrative, intramolecular ring-opening cyclizations in the presence of stoichiometric amounts (110 mol %) of $Sc(OTf)_3$ and/or $BF_3{\cdot}Et_2O$ to generate functionalized 1-aryl-1,2-dihydronaphthalenes in good to high yields (Scheme 2).[4c] Using this approach, Nishii has since highlighted the method's utility through the total syntheses of (±)-cyclogalgravin[4b] and (+)-podophyllic aldehydes.[4a] Despite the evident utility, Nishii's method exhibits several drawbacks that preclude it from being exploited by the greater synthetic community. First, the four-step synthesis of the precursors required the use of several harsh conditions and reagents, including SmI_2,[5] HMPA, and Jones reagent. Second, stoichiometric amounts of Lewis acid were required to promote the transformations. Finally, the substrate scope was limited. Toward overcoming these drawbacks, we disclose a calcium-catalyzed, dehydrative, ring-opening cyclizations of cyclopropyl carbinols to form (hetero)aryl-fused cyclohexa-1,3-dienes (Scheme 2).

Scheme 2. Dehydrative Ring-Opening Cyclizations



Mechanistically, Nishii's reaction (Figure 1A) is analogous to the formal homo-Nazarov cyclization of aryl cyclopropyl ketones (Figure 1B). In the formal homo-Nazarov cyclization,

Received: July 3, 2016
Published: August 12, 2016

DOI: 10.1021/acs.orglett.6b01933
Org. Lett. 2016, 18, 4218−4221

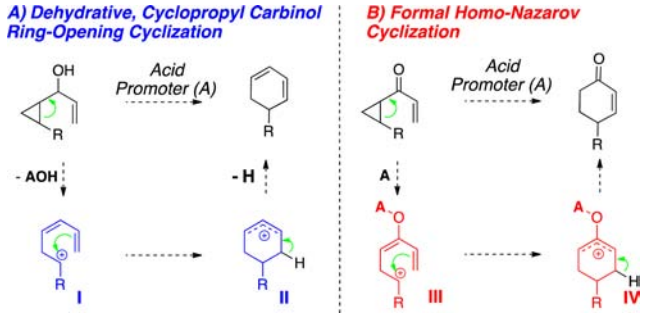
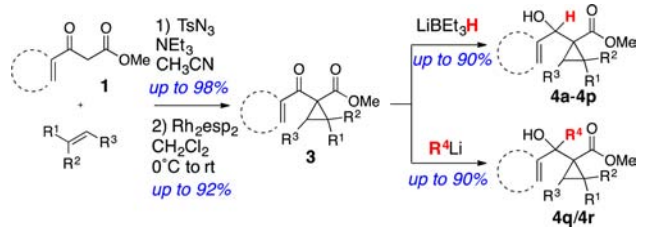


Figure 1. (A) Dehydrative, cyclopropyl carbinol ring-opening cyclization vs (B) formal homo-Nazarov cyclization.

acid-mediated cyclopropane ring opening affords an acyclic carbocation **III** that is directly analogous to allyl carbinyl cation **I**. Finally, intramolecular π-attack and elimination provides the resulting six-membered rings products via intermediates **II** and **IV**, which are very similar in structure. Over the past several years, we have established the catalytic, formal homo-Nazarov cyclization as a viable template for diversity-oriented synthesis.[6] Given the analogy between the two reactions and our interest in the catalytic formation of functionalized six-membered rings, we sought to directly address the drawbacks by (1) accessing the cyclopropyl carbinols by an alternate route, (2) identifying the appropriate conditions to promote catalysis, and (3) expanding the overall substrate scope.

To overcome the harsh conditions for substrate synthesis, we envisioned a straightforward path to the functionalized cyclopropyl carbinols **4** involving synthesis of the corresponding donor−acceptor (D−A) cyclopropanes **3**, followed by chemoselective alcohol formation (Scheme 3). This approach

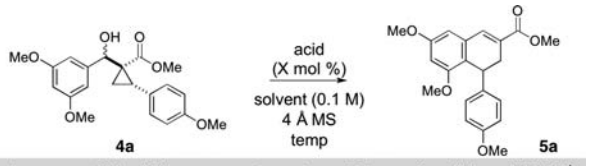
Scheme 3. Preparation of Cyclopropyl Carbinols 4



has a specific advantage over Nishii's synthesis of **4** in that the methods to access the D−A cyclopropanes are well-established, multigram scalable, experimentally facile, and highly functional group tolerant.[6b,7] Starting from the β-ketoester compounds **1**, diazo transfer, Rh(II)-catalyzed cyclopropanation, and subsequent reduction with $LiEt_3BH$ (or treatment with an alkyl or aryl lithiate) afforded the desired cyclopropyl carbinols **4** in modest to high yields for each individual step.[8]

To find viable conditions for catalysis, our investigation began with cyclopropane **4a** as the initial model system that was subjected to an extensive screening of both Lewis and Brønsted acid catalysts (Table 1).[9] Without an acid promoter, no reaction occurred (entry 1). When **4a** was treated with 15 mol % $In(OTf)_3$ or $Sc(OTf)_3$, the desired dihydronaphthalene **5a** was obtained with poor yields (entries 2 and 3). In contrast, modest yields of **5a** were afforded using 15 mol % of TfOH (54%, entry 4),[8] $Ga(OTf)_3$ (53%, entry 5),[10] and $Bi(OTf)_3$ (49%, entry 6).[11] After some further screening, we determined

Table 1. Initial Optimization Reactions[a]

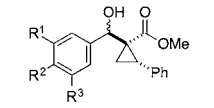


entry	acid (mol %)	solvent (temp °C)	time (h)	yield (%)[b]
1	None	CH_2Cl_2 (23)	24	--[c]
2	$In(OTf)_3$ (15)	CH_2Cl_2 (23)	24	28
3	$Sc(OTf)_3$ (15)	CH_2Cl_2 (23)	24	20
4	TfOH (15)	CH_2Cl_2 (23)	0.33	54
5	$Ga(OTf)_3$ (15)	CH_2Cl_2 (23)	1	53
6	$Bi(OTf)_3$ (15)	CH_2Cl_2 (23)	0.33	49
7	$Ga(OTf)_3$ (5)	CH_2Cl_2 (23)	18	61
8	$Bi(OTf)_3$ (5)	CH_2Cl_2 (23)	18	58
9	$Ca(NTf_2)_2$ (1) n-Bu_4NPF_6 (1)	1,2-DCE (84)	1	54

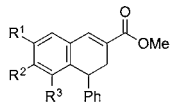
[a]Reaction performed with **4a**, indicated acid catalyst, 4 Å molecular sieves, and solvent at given temperature. [b]Isolated yield of **5a** after column chromatography. [c]No reaction.

that at 5 mol % both $Ga(OTf)_3$ and $Bi(OTf)_3$ generated higher product yields at 61% and 58%, respectively (entries 7 and 8).

At this stage, we intended to move forward with $Ga(OTf)_3$ as the preferred catalyst. Unfortunately, after some further optimization studies and a move toward probing substrate scope, we found that $Ga(OTf)_3$ was not the ideal catalyst.[8] In order to determine the optimal conditions, we compared the product yields for three different substrates after subjecting each to the following catalyst systems: (i) $Ga(OTf)_3$ (5 mol %), (ii) TfOH (15 mol %), and (iii) $Bi(OTf)_3$ (5 mol %). While each catalyst worked equally well for the formation of **5a** from **4a**, the catalysts gave inconsistent results for the reactions with cyclopropyl carbinols **4b** and **4c**. For example, $Ga(OTf)_3$ proved to be the least effective catalyst for **4b**, affording a complex, intractable mixture, whereas $Bi(OTf)_3$ and TfOH both gave >30% yield of the cyclized product **5b**.[8] In contrast, with **4c**, $Ga(OTf)_3$ provided 62% of the desired product **5c** at higher temperatures, while both $Bi(OTf)_3$ and TfOH both gave <30% yield.[8]



4b (R^1, R^3 = OMe; R^2 = H)
4c (R^1, R^2 = OMe; R^3 = H)



5b (R^1, R^3 = OMe; R^2 = H)
5c (R^1, R^2 = OMe; R^3 = H)
5c' (R^1 = H; R^2, R^3 = OMe)

While sorting through this conundrum, we became fascinated by highly Lewis acidic calcium complexes that have been pioneered by Niggemann[12] and others.[13] Abundant in the earth's crust, calcium is inexpensive and considered nontoxic even in large quantities.[12,13] In one series of relevant examples, Ca complexes have been shown to generate carbocations from alcohols (via C−O bond cleavage) that can be used to alkylate arenes.[12a,13c] After some optimization, we were pleased to find that the Niggemann combination of $Ca(NTf_2)_2$ and additive n-Bu_4NPF_6 (1 mol % each) effectively promoted the conversion of **4a** to **5a** (54% yield) and, ultimately, afforded the most consistent reaction outcomes (Table 1, entry 9).[8] For example, when **4c** was employed, the Ca complex generated **5c** in 76% yield (along with 9% yield of its regioisomer **5c'**) when compared to TfOH (36%), $Ga(OTf)_3$ (62%), or $Bi(OTf)_3$ (39%). Thus, based on the results for the three compounds, we

DOI: 10.1021/acs.orglett.6b01933
Org. Lett. 2016, 18, 4218−4221

determined that the $Ca(NTf_2)_2$/*n*-Bu_4NPF_6 complex at 1 mol % would be the optimal conditions for the remainder of the study.[14]

Next, the overall scope of the cyclization reaction was explored and summarized (Table 2). First, we examined a series of substrates incorporating the 3,4-dimethoxyphenyl moiety (as in **4c–l**) with varied substitution at C(2) and C(3) of the cyclopropane. 4-Methylphenyl cyclopropane **4d** gave **5d** in 93% yield as a 12:1 regioisomeric mixture (entry 4). 4-Methoxyphenyl cyclopropane **4e** cleanly afforded **5e** as the only regioisomer in 90% yield (entry 5). 4-Bromo- and 4-chlorophenyl cyclopropanes **4f** and **4g** each provided their respective dihydronaphthalenes **5f** and **5g** in 75% and 68% yield with a 10:1 rr (entries 6 and 7). The 2-naphthyl cyclopropane **4h** generated **5h** in 97% yield with a 12:1 rr (entry 8).

Disubstituted cyclopropanes were also tolerated under the reaction conditions. For instance, 2-methyl-2-phenyl-substituted cyclopropane **4i** gave **5i** with high yield and regioselectivity (94%, 19:1 rr) (entry 9). Similarly, the 2-methyl-2-(3-thienyl) cyclopropane **4j** provided **5j** in 86% yield with a >99:1 rr (entry 10). In contrast, indanyl-fused cyclopropane **4k** resulted in a more complex reaction mixture, and only a modest 31% yield of **5k** was isolated (entry 11) due to competing elimination of the acyclic, ring-opened cation (**I**, Figure 1).

Given that all of the previous examples employed (hetero)-aryl substituents on C(2) or C(3) of the cyclopropane, we were particularly interested in the compatibility of alkyl substituents. Unfortunately, when the spiro[2.4]heptane **4l** was subjected to the reaction conditions, an inseparable mixture was obtained that, based on qualitative NMR, contained 36% yield of **5l** (entry 12).

Removing the methoxy groups from the aryl carbinol substituent (as in **4m**) afforded **5m** in 40% NMR yield as a similarly inseparable mixture (entry 13). Placing one methoxy group in the 4-position (as in **4n**) still allows for cyclization to occur in good yield (63%, entry 14). Finally, exchanging the aryl carbinol substituent with a heteroaryl group (as in 2-benzofuran for **4o**) is well tolerated as the anticipated cyclohexenyl-fused benzofuran **5o** is generated in 65% yield (entry 15).

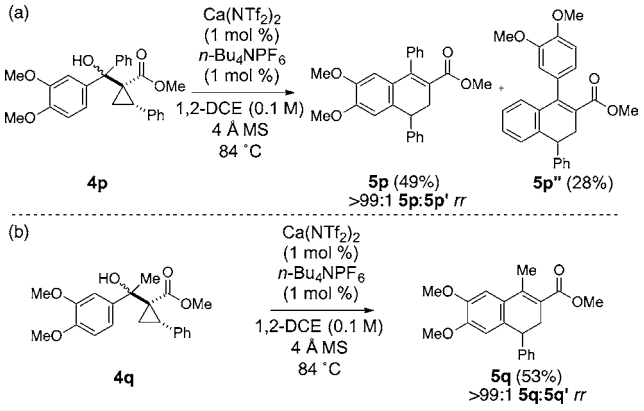
Tertiary carbinols were then synthesized and studied for their compatibility under the reaction conditions (Scheme 4).

Table 2. Reaction Scope

entry[a]	SM	product	yield of 5 (%)[b]	rr (5:5')[c]
1	**4a** (R = OMe)	**5a**	54	--
2	**4b** (R = H)	**5b**	26	--
3	**4c** (R = H)	**5c**	76(85)	8:1
4	**4d** (R = Me)	**5d**	86(93)	12:1
5	**4e** (R = OMe)	**5e**	90	>99:1
6[d]	**4f** (R = Br)	**5f**	68(75)	10:1
7[d]	**4g** (R = Cl)	**5g**	62(68)	10:1
8	**4h**	**5h**	89(97)	12:1
9	**4i** (R = Ph)	**5i**	89(94)	19:1
10[d]	**4j** (R = 3-thienyl)	**5j**	86	>99:1
11[d]	**4k**	**5k**	31	--
12[d]	**4l**	**5l**	36[e,f]	--
13[d]	**4m** (R = H)	**5m**	40[e,f]	--
14[d]	**4n** (R = OMe)	**5n**	63	--
15	**4o**	**5o**	65	--

[a]Reactions performed with cyclopropane **4**, $Ca(NTf_2)_2$ (1 mol %), *n*-Bu_4NPF_6 (1 mol %), and 4 Å molecular sieves in 1,2-DCE (0.1 M) at reflux. [b]Isolated yield of **5** after column chromatography. Yields in parentheses represent combined isolated yields of **5** and **5′**. [c]Ratio of isolated yields of **5** to regioisomer **5′** (if applicable). [d]Performed using $Ca(NTf_2)_2$ (5 mol %), and *n*-Bu_4NPF_6 (5 mol %). [e]Yield based on ^1H NMR using dimethyl terephthalate as an internal standard. [f]Inseparable mixture.

Scheme 4. Reactions of Tertiary Carbinols



Cyclopropane **4p**, containing both phenyl and 3,4-dimethoxyphenyl carbinol substituents, afforded two products **5p** and **5p″** in 49% and 28% yield, respectively (Scheme 4a). The minor product **5p″** arose from the competing trapping of the allylcarbinyl cation intermediate by the phenyl group. Cyclopropane **4q**, containing a methyl carbinol substituent, yields its expected product **5q** in 53% as the only observed regioisomer (Scheme 4b).

Lastly, the resulting products can serve as synthetic building blocks and can be readily derivatized. In particular, 2-carboxy

DOI: 10.1021/acs.orglett.6b01933
Org. Lett. 2016, 18, 4218–4221

dihydronaphthalenes **5** have been shown to undergo dihydroxylation,[15] aminohydroxylation,[16] epoxidation,[17] aziridination,[18] conjugate addition,[19] [3 + 2] cycloaddition[20] with CH_2N_2, and oxidation[21] with DDQ.

In conclusion, we have disclosed a calcium-catalyzed, dehydrative, ring-opening cyclization of cyclopropyl carbinols to form (hetero)aryl-fused cyclohexa-1,3-dienes in up to 97% yield. The overall merits of our approach include the following: (1) the utilization of earth-abundant calcium as the catalyst system with low loadings (1 mol %); (2) the first examples of catalysis for this type of intramolecular ring-opening cyclization; (3) a straightforward synthetic sequence to access the cyclopropyl carbinols from the corresponding D−A cyclopropanes; and (4) a broader substrate scope. Future work will include application of the methodology in natural product synthesis and the exploration of asymmetric variants.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01933.

Experimental procedures; spectral and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.F. gratefully acknowledges financial support from the National Science Foundation (CAREER Award CHE-1056687). M.S. thanks Georgia Tech for a GAANN graduate fellowship. We acknowledge Corey W. Williams (Georgia Tech) for his essential assistance with manuscript revisions.

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(8) See the Supporting Information for more details.

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(14) Although Tf_2NH does promote the reaction, it provides poor regioselectivity and/or greater side reactions (particularly degradation) when compared to the Ca-catalyzed reactions. For instance, at 1 mol % of Tf_2NH with **4c**, the reaction does not reach completion, and only 45% of the cyclized products are obtained. Moreover, the results from the Tf_2NH reactions vary from substrate to substrate. In some cases, it requires higher loadings (>10 mol % vs 1 mol % with Ca) to achieve similar product yields. However, at this time, we are unable to rule out the possibility of a synergistic Lewis and Brønsted acid effect, especially given the elevated temperatures that may facilitate formation of trace amounts of Tf_2NH. See the Supporting Information for more experimental details.

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DOI: 10.1021/acs.orglett.6b01933
Org. Lett. 2016, 18, 4218−4221